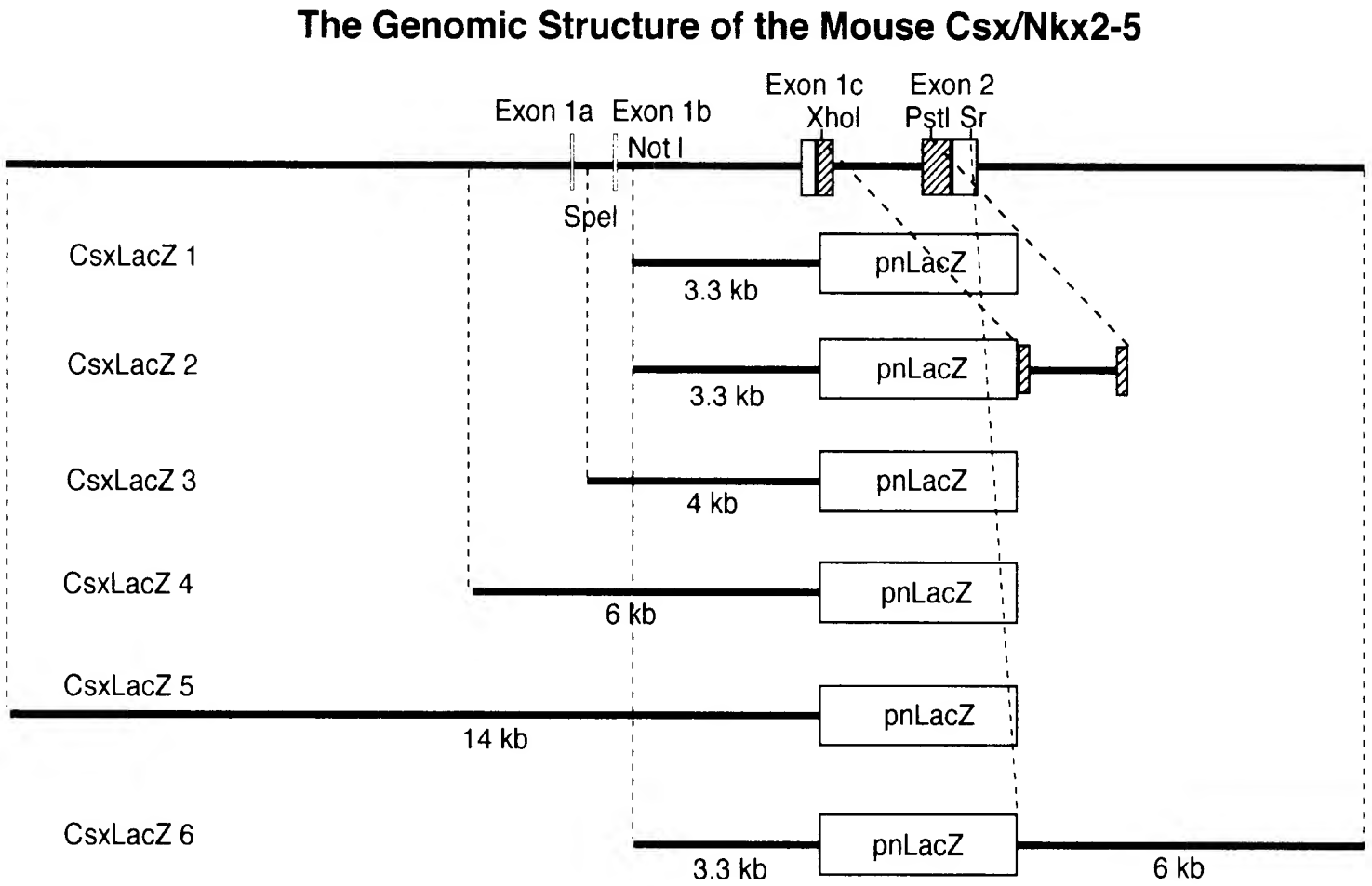
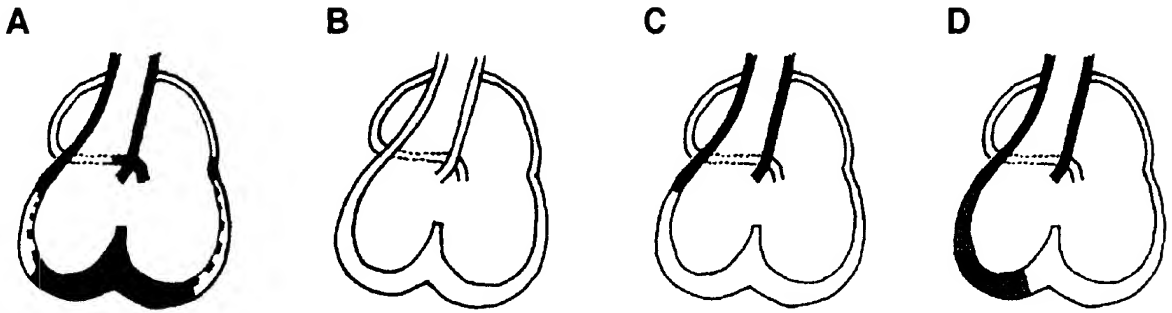
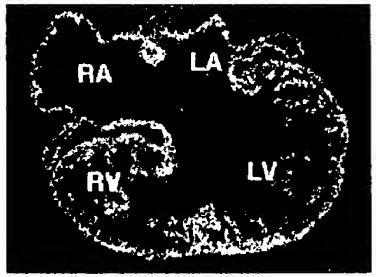
FIG. 1



The Locations of the Csx/Nkx2-5 Cardiac Enhancers



Endogenous Csx/Nkx2.5 at E10.5



Csx/Nkx2.5 locus

A	B	C	D
Cardiac crescent RV medial wall and inner trabeculae LV medial wall and inner trabeculae interventricular septum	dominant repressor element	RV base and outflow tract	RV lateral wall

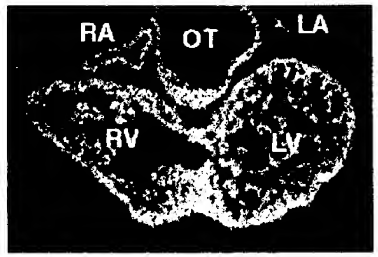
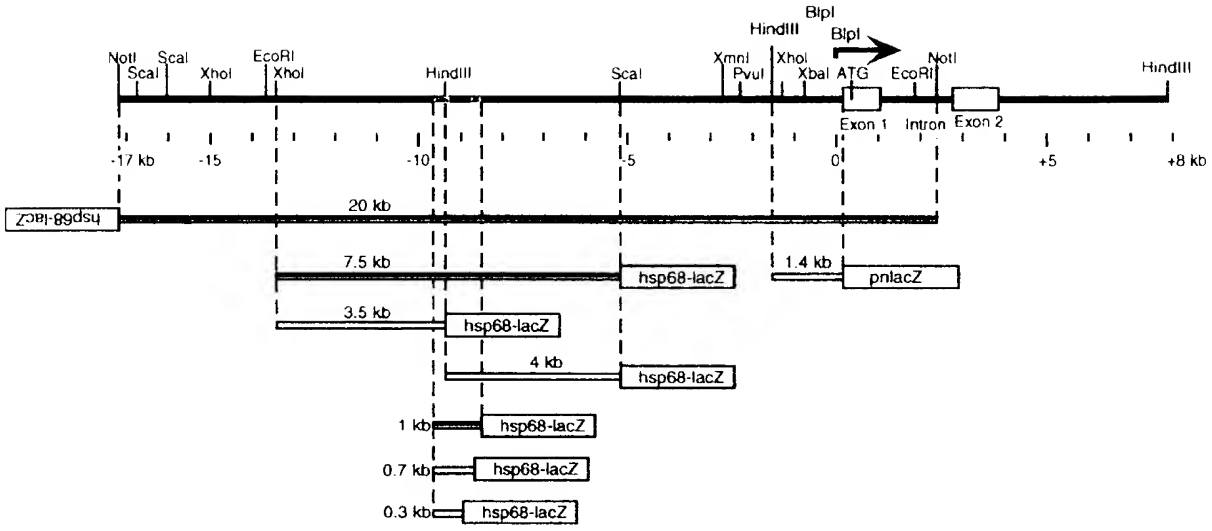


FIG. 3A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ScaI
XhoI
EcoRI
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HindIII
BlpI
ATG
EcoRI
NotI
HindIII
Exon 1
Intron
Exon 2
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-15
-10
-5
0
+5
+8 kb
hsp68-lacZ
20 kb
7.5 kb
hsp68-lacZ
1.4 kb
pnlacZ
3.5 kb
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4 kb
hsp68-lacZ
1 kb
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hsp68-lacZ
0.3 kb
hsp68-lacZ


Human 1 TAGGAAAAAAAAAAAAAAAGGAAGCCCTCCGGGAGAGACATGCGCCCTAATATTTCTCCCAGATGGGCCGGGTTCAAGCGCGTTTGAGAGTTTGCTCTCCT 100
Mouse 1 CACACAGACAAGCAGTCAATGCGCTGTTTGGCTGTTCCTTGTGTT----TGTGGTTGAAAAGCGGTCCACACACACCCGT-TCTGAGTGACAGTGTGCC- 95
<Sp-1
Sp-1>
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Mouse 96 -CCAGTGACCCGCTCT 185
Human 201 300
Mouse 186 285
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TGF-b>
<MEF2
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Mouse 286 385
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Human 400 498
Mouse 386 485
Sp-1>
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Mouse 486 GATCCCTGGGAGCGCAGAGACGCCTTTCTACCGGCAGAGACTGAAGTTTGACTGGAGCGAGGCGGGGCGGAGCCACCTCCCGGTCCCCGTGCACTCCGGA 585
<Csx
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Mouse 586 ATTGTGAACGCTCCCGCAAAGTCCCCGCGAGTGTTGTGTTCACACTAATTGGTGTGCCTCTGAGTTCC---------- 653
Human 699 CCTGTGTGTACCCGTGTCGTTTTAGCGAATTTAAAGCACATCAGGCCGGGCGCCATGGCTCACGCCTGTAATCCCAGCACTTTAGGAGGCCGAGGCGGGC 798
Mouse ----------
Human 799 CGATCACCTGAGGTCGGGAGTTCGACACCAGCCTGGCCAACATGGTGAAACCCTGTCTCTACAAAAAATACAAAAATTAGCCGGGCATGGTGATGCGTGC 898
Mouse ----------
Human 899 CTGTGATCCCAGCTACTCGGGAGGCTGAGGCAGGAGAATCGCTTGAACCCGGGAGGCGGAGGTTGCAGTGAGCCGAGATCACACCACTGCACTCCAGCCT 998
Mouse ----------
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Mouse ----------
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E-Box>
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Mouse 654 ATCCGTACTCCCCCCCCCCCCAAGTTTAAA 743
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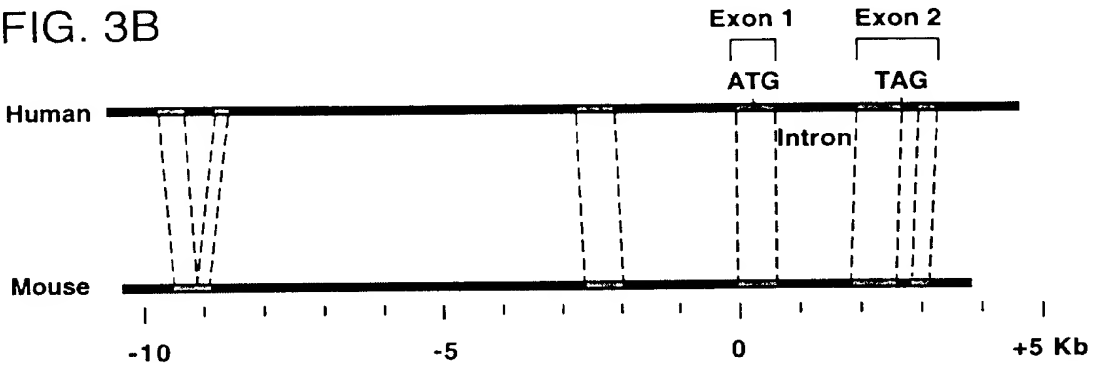
Mouse 744 GACATTGTGTTCCTCTAGCGTCTCCATCCCGCTTTTCACCAATTCGTGCCCTGGCCGAATCCCGTGGGAGCAGAGGTGGCCCCTCGAAGTCCCGGGCCAC 843

FIG. 3B

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Mouse     1 GAAGAGAAAGGCCAGGGCCTT-TTCACCAAGGTTGTAG-GGGTGGGAAAGTCACTGATTTTGTTCAAATTAGAAGAGTTTT-----CTTCCTTTTTCTTG  93

Human    97 ACACCTGACCCACAGGACTGACAGTTCTAGGAAGCCCCCTTACCCGAAAATAGGAAATAAATCCTTGCCACCTTGATTTGCAAGGGCAATGCTAATTTTT 196
Mouse    94 ACACCTGACCCACAGATTTGTCAACTCT-GGAAGCCCTTATATCCGAAAA-AAGTGATAAATCCTCACCACATTGATTTGCAAAGGAAACG--------- 182

Human   197 TTCTTTCTCCAGAGCTCTCAAAAAAAAAAAAAAAAAAAACCTTACTAAAAACAGGGATCCCGGATGTAGCCTCGATGTCCCCCATTAAACGGTAATATTTC 296
Mouse   183 -TCCCCTCTCAAAACTATTTTTTAAAAAAGACTTAAAACAGGGATCCCGGATGGGGGCCCCAATATTGCTCC------CCCAATTAAACGGTAATATTTC 275

Human   297 AGGCGTCCGCTCACACTAATCTTTCAAACTGTCATCGCGAGCCGCCTGGCCAGCAGATTCACTT-AACAGCGCTCCCAGGACCCTCGTTCCGAGCTCTTT 395
Mouse   276 AGGCGTCAGCTCACACTAATCTTTCAAACTGTCATCGCGATCCGCAGGGGCAGCCGATTCACTTTAACAGGACTCCCAGGACC-TCGCCCGAAGCTGTTT 374

Human   396 TCAGCGAGACATTTAATTGAATCGGATGTGGCTCGTTTGCCAGACGTCACCGCCTCGGCGATAGGCATCCTCTCCAACGACACCCCCCCCCGCCCGCGCT 495
Mouse   375 TCAGCAAGACATTTAATTGAATCGGATGTGGCTCGTTTGCCAGACGTCACCGCCTGGGTGATAGACATCCGTCCAACCCACACAAACCAATCTTCAATCT 474

Human   496 CGAAAACAATCTTCA  510
Mouse   475 CGGGAGGGTCCCAAGC 490
```

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Human     1 TAGGAAAAAAAAAAAAAAAGGAAGCCCTCCGGGAGAGACATGCGCCCTAATATTTCTCCCAGATGGGCCGGGTTCAAGCGCGTTTGAGAGTTTGCTCTCCT 100
Mouse     1 CACACAGACAAGCAGTCAATGCGCTGTTTGGCTGTTCCTTGTGTT----TGTGGTTGAAAAGCGGTCCACACACACCCGT-TCTGAGTGACAGTGTGCC-  95

Human   101 ACCAGCCTCGGGTTCTAGGCCCCCCGCACCCTCATCCTGGCTCCCGCCCCTTCTCTCCACCCTCCCGGACCCCTAAAGGGGCGGCGGGGCCCA AGCCGAG 200
Mouse    96 -CCAGTGACCCGCTCCATGTCCCA-GAATCTTCATGCGGGCTGCAGCATCTCCTTCCCACCCTCCAGGAAACGC--GAAGGACAGCGG------ AGCCGAG 185

Human   201 GGCGCTGCGCCTGACCCCGAGCGGAAGGGCCCCAGTCTAGGTCCTAATGCGGGTGGCGTCTCCTTTGACAGGCGGCGTTTGGGGACAACAGCGGGGACGA 300
Mouse   186 GGGGCAGCGCGTGACCCCGAGCGGAAGGGCCCCAGTCTGGGTCCTAATGCGGGTGGCGTCTCTCTTGACAGGCAGCGTTTGGGGACAACAGCGGGGAAGG 285

                GATA>          <dHAND  TGF-b>                                    <MEF2
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Mouse   286 GAGATAAGATGACATACCAGAGCAGATTTGGTGTGCGCGCTGATACTCCTGGCCCGACAGGAAACTCGGAGCTATTTAAAAAGGCCCTATCGATTACTTT 385

          <GATA
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Mouse   386 ATCTTCCCCGGAGGAAATCTTGCCGAGAGACAAAAGATGTCCCCCTACCTAAAGATACAAGGCCACACAGCAGAGGGTTTGTACAGGCGACGCGCGAGTA 485

Human   499 GGCGCGGGGAAAGCAAAAACACACTGACGCTTAGAGTGCACAAACGTGTGTGTTCCCAGAGCAGCTCCAGAGTGCGGCAGGGACGCTGGGGGCGGCGAGG 598
Mouse   486 GATCCCTGGGAGCGCAGAGACGCCTTTCTACCGGCAGAGACTGAAGTTTGACTGGAGCGAGGCGGGGCGGAGCCACCTCCCGGTCCCCGTGCACTCCGGA 585

Human   599 GGCACCCACAGTATGGTCTTCTGTGCCCTTGGAAAGTTTTTTTTCACCGTATGCGCGTAAAACACGCACACACAGAGAAAGTGACTGTGCACTTAGGGCG 698
Mouse   586 ATTGTGAACGCTCCCGCAAAGTCCCCGCGAGTGTTGTGTTCACACTAATTGGTGTGCCTCTGAGTTCC---------------------------------- 653

Human   699 CCTGTGTGTACCCGTGTCGTTTTAGCGAATTTAAAGCACATCAGGCCGGGCGCCATGGCTCACGCCTGTAATCCCAGCACTTTAGGAGGCCGAGGCGGGC 798
Mouse     ---------------------------------------------------------------------------------------------------

Human   799 CGATCACCTGAGGTCGGGAGTTCGACACCAGCCTGGCCAACATGGTGAAACCCTGTCTCTACAAAAAATACAAAAATTAGCCGGGCATGGTGATGCGTGC 898
Mouse     ---------------------------------------------------------------------------------------------------

Human   899 CTGTGATCCCAGCTACTCGGGAGGCTGAGGCAGGAGAATCGCTTGAACCCGGGAGGCGGAGGTTGCAGTGAGCCGAGATCACACCACTGCACTCCAGCCT 998
Mouse     ---------------------------------------------------------------------------------------------------

Human   999 GGGCGACAAGAGCGAAATTCCGTCTAAAAAAATAAAATAAAATAAAATGATAATTAAGCCCATCAACTCACATTCAAAGCGGTTACTGGTGGTTGTAATG 1098
Mouse     ---------------------------------------------------------------------------------------------------
```
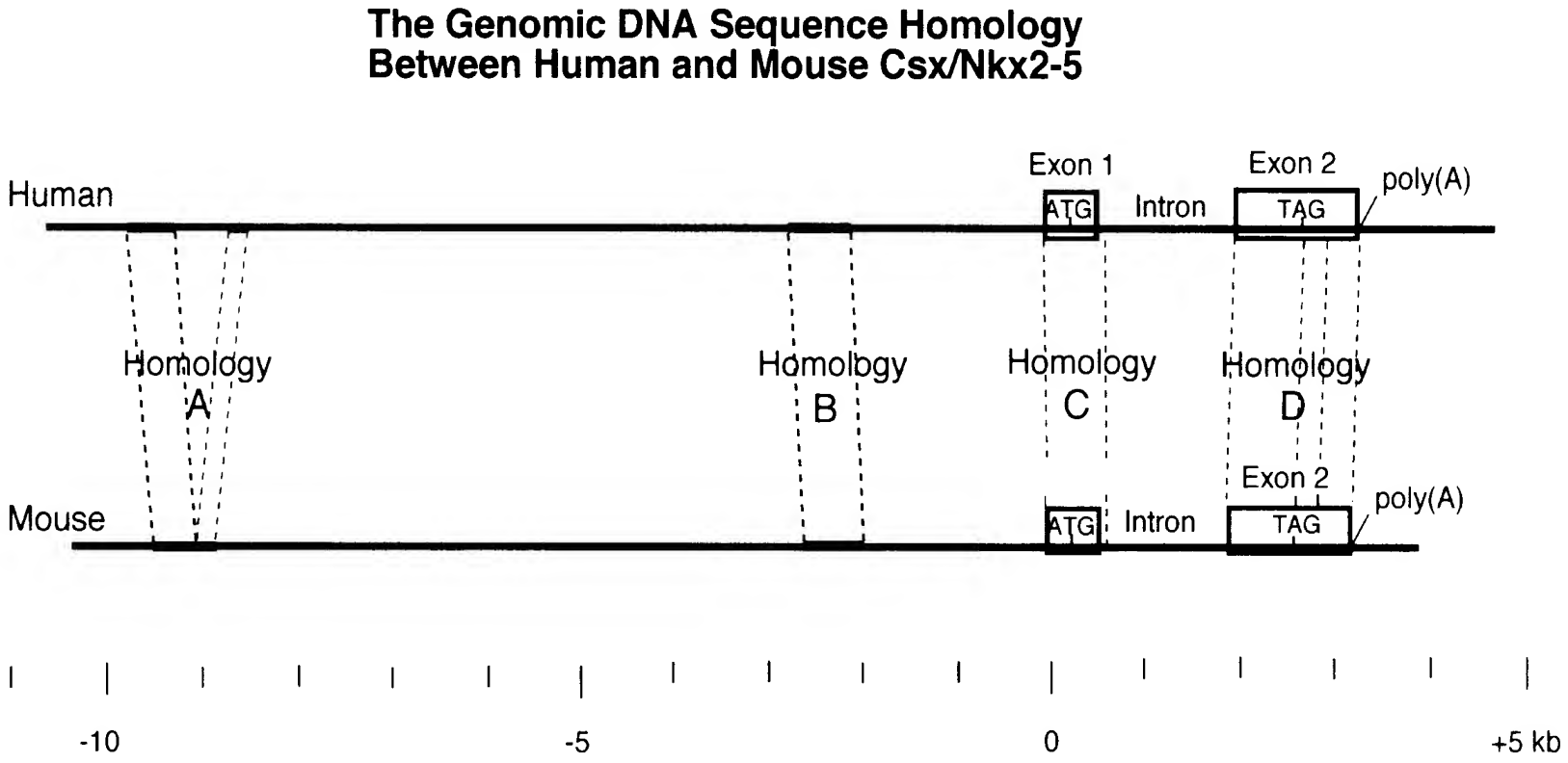

FIG. 3C


The Genomic DNA Sequence Homology
Between Human and Mouse Csx/Nkx2-5
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Exon 1
Exon 2
poly(A)
ATG
Intron
TAG
Homology
A
Homology
B
Homology
C
Homology
D
Mouse
Exon 2
poly(A)
ATG
Intron
TAG
-10
-5
0
+5 kb

FIG. 4A (1)

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TCTCTCTCCACAAAAAATTTAAAAACTAGCCAGGTGTGGTGGCAAACA
CCTGTAGTCCCAGCTACTCAGAAGGCTGAGGTGGGAGGATCACTTGAG
CCTGGAAAGTAGAGGCTACAGTGAGCCGTGATCACACCACTGCACTCC
AGCCTGGGAGACAGAGTGAGACCCTGTCAAATAAATAAACAAACAAAT
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TTTGTAAAGATTTTTAAAATGAAAATTCCCAAATTGCTTTCCAGAAGG
ATTGTTCAAAATTATACCCACATTTCACTCATGTTCTCTTCCTGAACA
GCAGCAATCAGGAAAAACTCCCTGGAAGAGGCAGGGCTTAGACTGAGA
TTTTAAAAGGGGGTAGGCCTCAGCTCTCCTTCCAGGTTTACACTGTGC
ATGTTTCCAAACTCAAAGAATTTACACTCTTCTGGTTGCATTGCTCTG
TAAAGATCTGACCCACTACTATGTATTAAAAAGGGATGCATGATAATG
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GTCAGAAGTATGTCACTAGACCAGAGCCAAAAATAGGTGCTATATCAT
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ACGCCCCCACCAGAACGGCTTAAAATCTAAAACATGTAATACCGAATG
TTTGCAAGGATGCGGAGAAACTGCCATTTTTGTACACTGCCAGTATGA
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ATTTACCCAACAGAAATGTGTAAACATGTTCACCAAAAGACACACGCA
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TACAAACAATGTGATTGAACCTCACAAACATATACTAAGTAAAATTAT
CAGACACAAAGAGTGTATATACTGTATTTAGATACATGTGAAGTCTGA
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TGCTTCCTGAACTGCATGCTAGTGAGGCAGCTGTTATTTTGTGCAGTC
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GCAAGTGGAAGCAAGTACACTGCTGGACTTGGCTGGGAACTTAGGGGA
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GCAAGGCAGGATTCGGGAGTGGCTGAGAGTTTTCCCAGTGCCACCTGG
TCCCACCTCCCCTCTCCCACTTCTAATGAACGGGCAGTACAGCTTCTG
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GAGGGCGATGCACTGGGGTCCTCACCTACACCCCCCTTGGCTGTCTCA
CCACTCTGAATTATAAATGCCCGGACTTCCTCATCTCCCACCCACACA

FIG. 4A (2)

TCTTGTTAGAAGAAAAGAAACGAATCTCCCAGGGCTCCTTCTAACAAA
AGTGTTCATTCAGAGTAGCCCTGCTTGAGGGCCCCTGGCCTGGAGGAG
TGGGAGAGGCAGCCCTCCCCCTCCAGGAGAGTCATCTCCAGGGCTACC
CAGGACTGAGTAACTAGGTCACCAGAGTAACCAAAGAGGCAGGAGACA
AGGGCATTCAAGCATTGGGCCAGGAATGGAGGGTGATGTCCAGTTCAT
GTTCTTCTGGTTCCAGCATAGCACACGGTGCAAATGAACCATCATGCA
AGAAAACACAGCTAGTCTCCCTTCCTCCACCAGCAACCTTTGGTTACT
GATAATAATCAAATTCACTATTTTTTTTTTTTTTAACTAAGGCTGAG
ATAATGTCAAAGGACCACAGGGAATAGGAAGGCCTAAACCAAGGCCTT
AAAGAATGAGAAGAAGATTCATTCAAAAAAGCCTCCTAAGGGAGGAAG
ATGTTTTTCCCTCCTTTACTTTTCTACAGTAATTTTTATTTTGGATAA
ATAAACCCTGATAAATGAGAACCCACGCTTTCCCAAGGCCAGGCTGTG
TTTTGGTGGGTGGTCCTCCGTCAGCAGTTGGAGTAATCCAGAGTGATC
CCGGGCAAGTCGGAAGGGAGCAAGTCTGTGTTGAAGCCAAGAGGTATC
TTTCCCTACAGCTTCTCAAGAGAGGGGATCCCCGTGGGTAATTGTGAG
GCTGGAAACACCGAGAGGCTGACTCCCATGTTTATAGAGGTCATTGAT
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ATACAGAAAATGAAAAATGAGGAGATTTGCATAACAGCGCTTGGACGT
CTGAAGGGGCCCAGGGCCTAGCGGCTGGTGGGGCACCTAGAAACACTT
CTGCCTGCAGATCGCGGAGGGTTAGCCACAGGAAGGGGTCGCCTAGGC
TGGCCACAGGGCCTTTGCTGTGACTGAAGGACCAGCCTTGGCGGCACC
TTCTTTCCCCTCTGCCCTGCACTCCGGCCCCGCCGGAGTCAGAGCTGA
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GTACCCGTGTCGTTTTAGCGAATTTAAAGCACATCAGGCCGGGCGCCA
TGGCTCACGCCTGTAATCCCAGCACTTTAGGAGGCCGAGGCGGGCCGA
TCACCTGAGGTCGGGAGTTCGACACCAGCCTGGCCAACATGGTGAAAC

FIG. 4A (3)

CCTGTCTCTACAAAAAATACAAAAATTAGCCGGGCATGGTGATGCGTG
CCTGTGATCCCAGCTACTCGGGAGGCTGAGGCAGGAGAATCGCTTGAA
CCCGGGAGGCGGAGGTTGCAGTGAGCCGAGATCACACCACTGCACTCC
AGCCTGGGCGACAAGAGCGAAATTCCGTCTAAAAAAATAAAATAAAAT
AAAATGATAATTAAGCCCATCAACTCACATTCAAAGCGGTTACTGGTG
GTTGTAATGTATCCATAGACACAGGTCTAAAATGTAAACGCTCCATTG
TGCTCCTTTTAAGGGCTTGAATGTCTGCAACTGTCATGTGTACACTTA
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TCTGAATCCCCGCATTTCGCCAATTTGCTTGGAGCGCAGAACGCCCTC
CGCGAAAGGCGGCTGCTGATCCCGACTTTGCTCCGGTATCGCGCAGCT
TGTTGGCCTCCGGGTCCCCCGTGCCATGCCCCCGGGAGGCTCTCCACA
GACACCGCTTGCGCCGAATTATACGAGACTGAATGGGTTTTTTTGGTG
TGTGTGTGCAACACAACAATTTGTCAGCTGCTGTTCACAATGCGCTCC
GCCGGGCGGTGGAAACTTGGCTGCGGTAACGCACAGCAGGTTGGAGGG
CACGACCCGGAAGGAAGGAAGAGGCGAGGAGGGAAAGGCGGCGACCCT
AGGCCCGCTGGCCAGCCGTTTCCAGCATCAATTCAGCACTGAGCCGGC
CGCAGCAGCACAGGGCTGGGGGCTCCCGGAAGTTCGGCCAGCCGGGGT
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CAAAGTCGCGGTTCCCCGGGCTTCACACCCGCCGGGCAGGCGCGAACC
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GGGACTCCGAGGAACTGATTCCAGCGTCTCGATTCTCTCCGCCTCTCC
GCCCGTTTTGGCTGAAGCGGTTTGCAGCCGTCGGGGCAGAAGGGGTGG
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TTGATTATGGTGGCTGTTATGGGGGTGCACATCCAAGTGTCAAGACTC
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GATTTTAAACCTAAATAAGCCAGGTAACAGCTTTGCCTGGGTGGCTGG
GGGAGAGGCTTGGGACACTTTACATTGATCTCCCTCTTAGGCATGTTC
GTTTTGGTTTGGTTTTGTTCTTATGATGTATTATTTATTCAAAAATAT
ATCATTAGCAGAGTGACTGATGTAAATGTAAAACCATTGTTAAGGAAA
CCAACAAAAGCGGGAACAAGAGACACTGGTGCATCCTGTTAGAGGGAT
AAGAATAAGCACTCGCTGTCCAAGCTCATAAAATATTTTGGGAATGAA
TGTCGTTCCGCTTTGTTTTTTTGGTTTTTTTGCTCATGTGTTTAACAT
CAACGAGAAATGAGGACCCAAAACTTATCCAGTGGTTACGTGTGGTGT

FIG. 4A (4)

GTGTGGCTGTCATCTCCTTGGGACTGGCTACTGAAGGCCACAGGCGTG
GGAGGACCAAATGCTCCCTGGATGTTGAGTCCCAGCCGGTAAGCAGCA
CACAGTCCCGCTTGCAGCAAAGATGTGGTGGCCGGCTGCGCTGTGGGG
GAAGGCCAGGCCCGGACAGGAACCTCAGATCTCACCGGCGGATGAGAG
TGGTGCCCCCTGCAGCTGGAGTCCCTGCTGGCCTGAGAGCTCCAGCTG
TGCCACCGTTGGGCAGACCCCACACTTCAGGGAGCTGCCAGGATCAGT
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TGCGGGGAGCGCCCGGGTGGGGCTACCAAGGCCACAAGCCAGTTCCAT
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TGACCACAAGACTTGGGCCTGCCCTCTAGTTTGTCTATACCTGCCCCC
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ACCACCCTGCACAGTCTTCCTACACCAAGGGCTCCGGTGCCACCCCTT
CACAGAGAGTTCACTGCACCGCTGCTTCGGCTGCCTGTCTCAAACCAT
ACACACACCTTTGATTCTTAAACTCCAAGATTAGGATGGGCCCCAGAA
ATCTGCATTTTTAATATGTACCTCAGAGGATTCTGGCCTAGATATTTC
TACAGCCCCAAAAGTAACAAGGAACCTGTTCCAAAAAGTGTATTACGG
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TGCCCATATTTAAAATACAAATTCTGCACCTGGTTTGCTATTTAAAGT
ATCTCAAAACATATCCATAAGAATACATATGAATGGAACTAATTCTTT
CTCATGGGATATGGGATCTGTTCTATGGACAACATAATTTTTAACCAG
TCCTAGTATATATACACTGGTTTTTTACATGTTGATCTTAAAAAATAA
AAACGGNTGAAA (SEQ ID NO.: 4)

FIG. 4B (1)

CAATTTCTATTNAGTTCTATTAAAAGGGATTTTTTTTNAACTCACTGGNAACCAGGAGGA
CTGNAAAGAAAAGTGAAATGGCTCTGGGACTTTCCTCTAAGGAGACCAGCATGGGTCGCC
CCAATTTTTATTTTGCACGTATTTGTCCGTTTTTGCCCCATCTCCTCTCTCCTGAAACAC
CAAGACCTTTTTGGAAGCCAAGAGAAATCATTACCCGATTCACAAAGAGCATAGAGAGTG
TAACAGTCACTGATCTTGTTCAAATAGGGAGAGTTTTTTTTCCTTCCCTTTTTGTAACAC
CTGACCCACAGGACTGACAGTTCTAGGAAGCCCCCTTACCCGAAAATAGGAAATAAATCC
TTGCCACCTTGATTTGCAAGGGCAATGCTAATTTTTTTCTTTCTCCAGAGCTCTCAAAAA
AAAAAAAAAAAAAACCTTACTAAAAACAGGGATCCCGGATGTAGCCTCGATGTCCCCCAT
TAAACGGTAATATTTCAGGCGTCCGCTCACACTAATCTTTCAAACTGTCATCGCGAGCCG
CCTGGCCAGCAGATTCACTTAACAGCGCTCCCAGGACCCTCGTTCCGAGCTCTTTTCAGC
GAGACATTTAATTGAATCGGATGTGGCTCGTTTGCCAGACGTCACCGCCTCGGCGATAGG
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GAAGGGCCGCAAGGCCGCTGACATGCAAGCTCCGTCCAAGAAGAATTTGGGTTGGAGGTG
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TCCACAGACTAGACTAACAATTCCAGACCCCCAGTAGTCCCTGGCTCAGAAACTCGAGGC
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AGGGCGTTGCGCGCCTCCTGGGCTGCCCTGCGGGGCTCACCTCTCTCCCCAGCATGGAGG
CCCCAGGTCCTGGGAGTGTGGCTTTGATGAGGGACAGGAAAAGTCCCAACATCAGGCCAA
TGCTTGACTTCACTTGCGTCGGCGTCTCAGACGGCACACTGTCGGGTTTGAGCACCCAAG
ATGTACGTTCTGGACAGACACTATTTTGTCCCCATACATGGAGCGTTTCCTCCGCACCTT
GGGCGCGCCTGCGGGAGCTGTGTCTTTAGGTAGTTTTTGGCCCTGCGCCGCCTTTATTCT
ACTCCAAGCGCTCTTTGCCAAACCCGCACTCCGCAAAGAGCCAAGCCCTCCACATCCCCA
TTCTCAGCAAGTCCACGCGTCCCGCCCAGCTTCCCGCCCGCGGTTCCCTGTACCAGCTAG
GGCCGTGAGAAGCCAACGCTTTTCCACTGACAAATCCTGTCATCCCCAGCTCTAGAAGGC
GTCCTTAACCTGGGCCCGCTCTGCCTGCCCGGACTCCTGAATTGTAAGCAAAATAAAACT
CCTCTCTGCAGTGTTCTGGGGAATGGAGAAGACCCCAAGCTTTCATCAGACCCTCCCAAG
GAGTGCGGGGACCCAGAGAAATGAGGCCACCCGGGCAGGATCTGGCCATGTAGCTGGCGC
TCCTGAAACTCTGGCAGATTTGTCTGACTTCTGTGCCCTACTCTACTGACCCTGGGCTAA
AAATGATCATGATCACCCCACTTGCCCTGCCCTTCCCCCACGCGCCTGACCGAGCCGCAG
GGGTGCCCCACTGGAAGTCCGGCCCAGAGGCCTCAGAGAAATCCTGGCCTAGCTGGGCTC
AGAGGAGCCCCGCCTCCCTGAGAGCTAAACCTGGGCTAGGACCCTGAAACCTCGAGGTTG
GCAGAAGCCTGAGGGCCTTGCTGCCAGGCAGGGAGGGCACGGGAAGGAGGGAGGTGGGAT
CGATGGCCTCCAAACAGGGGAAACAAGGTGGCTGGTAGCTGGGGCACTCCACAAGACAGG
TGTNTCCTGGGAAGCTGAGCTTACCAGCTGGGATTCCTGATTTATTTCATTATTAAGGGG
AGAGGCATTTCCCCTGGGAGGGTACTGGCAGTGACTGATGCCCCCTGGAGTTGTGCTGTG
CATAACACTACTGTAGGAGGCAGCAACTCCTACCCCACCTGGCCATCACTCACCTTGCCC
TTACTTTCGTTGATTCGCCCAGAAGCACCCAGAGCCTGCGGCATGATTGACCCTGTAGGC
CAAGCCAAACCAAACCCCCGAATTGTCCAGAATTTTCGCCCTGGTGTATCCCCAAAGCCC
AGCCCTGTCTTTNAGGGTTTTTTTCCTATTGAGATTTTCCCTCATCCCACCACCTTTAGT
AATAAAGCCTTCCTCAAACTAATTTCCTCCCCACCGCTTCCCACCCCATCCTTTTTTTTT
CCCATGCTGGTTTGGGTGCTGAGGAATATTTTTTCAAACCCACACCCATCCAGCCCTGCC
CAGAGGCCTGACTTTGCATGCCTCTGGTAGGNTTTTCAGGGTTACATTAGGGAGCAAAAG
CAGGGTGCAGGGGCAAAAGGGGACCCTTCCAAATGGGTCGTGGCCCCTTTAAAAAAGCTG
GGCAGGGNTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTGCCGTATGACTATA

FIG. 4B (2)

TTAGGTGACACGAAACTGCTCATCGCTCCTGTCATCGAGGCCCCTGGCCCAATGGCAGGC
TGAGTCCCCCTCCTCTGGCCTGGTCCCGCCTCTCCTGCCCCTTGTGCTCAGCGCTACCTG
CTGCCCGGACACATCCAGAGCTGGCCGACGGGTGCGCGGGCGGGCGGCGGCACCATGCAG
GGAAGCTGCCAGGGGCCGTGGGCAGCGCCGCTTTCTGCCGCCCACCTGGCGCTGTGAGAC
TGGCGCTGCCACCATGTTCCCCAGCCCTGCTCTCACGCCCACGCCCTTCTCAGTCAAAGA
CATCCTAAACCTGGAACAGCAGCAGCGCAGCCTGGCTGCCGCCGGAGAGCTCTCTGCCCG
CCTGGAGGCGACCCTGGCGCCCTCCTCCTGCATGCTGGCCGCCTTCAAGCCAGAGGCCTA
CGCTGGGCCCGAGGCGGCTGCGCCGGGCCTCCCAGAGCTGCGCGCAGAGCTGGGCCGCGC
GCCTTCACCGGCCAAGTGTGCGTCTGCCTTTCCCGCCGCCCCCGCCTTCTATCCACGTGC
CTACAGCGACCCCGACCCAGCCAAGGACCCTAGAGCCGAAAAGAAAGGTGAGGAGGAAAC
ACAGGCCCCCTTCTCCCCTCCTGGGTCGCTTTCGTCCCCAAGAAACTCAGGGCCAGGAGG
AGGACACACGCGCCCTTGGGCCGAGGGCTGGGCTGCGGCGGGGGGTTCAGAATGTAAGAT
GCCTGGTGTTGTCGCCAGGCTCCCGCGCCCCGCGTCCAATCGGAGGTTCAGAGGAAATGC
CGGATTGAAAGGATCCGAAAGCAAGAGACCAAAAAACTTTTCCCCCCGGCCTAACAAACC
CCCGGCGGTTTCCGCTCTGCTCCTGGTTCTGGTAGAATTTTAAAAATCGGTTTATGGTTA
AACAAAACAAAAAAACAGCCAAAACCCCCGTTTTTTACCCCCCCCTTGGATTTTCAAACC
CTTTTTAAAATTTTTGAAAAAAAACCCCCAAACAAAATTAAATTTTTTCCCCCAAAAAAT
TTTTTTTTTTAACAAAAGGGGGGGTGGAAAATTTTTTTTTCCCCCCCCCAAAAGGGGTT
TTTGTTTTTTTTTT--------TTTNTTTGGCAAAAATGAATTNTGGANCNAGGCCTTAT
TTNAAATGGATATTGGGNCCNCAGGATTTTGATTTCATTTATTTTTTTAAGCAAACTTNC
CGGGCCGGCAAGGGGAAAGGTTCCCTCGTGGAAAAGTAGGAAATGCTGCGCTACCGCGGG
CACAAGGNAGTGGACGAGATGAGTGCGGGATCATCCCGCAGGCCATCCCAGGATCGGGGA
GGGAGGCCGGCCCCGCTGCAGAAAGGGGCTTCTGGGAGACCCCCCAGCCCAAGGCAGGAG
CCCGGGCGATTCCCGGGAGGCCGCAGGCGCTGGGCGAAGCGCTGGGCGAAGGGCCGCTGC
CAGCCGGGAGAGAATTCATAGGTTTGTTGAGGAGCAGAGGCCTGGGAACAAATTCGGGCG
GGCACGGCGGCTAGAACTGATCGCTACCAATTCGAGGAAGCCAGCAAGGCAGGTTCCGAG
GCCGCCTGCCCACCCGCAGCTTCTTGGACACTGCGCAAACCCTGCTGCGGCCAGGCTGGA
GCCTCCGATCACCAAACCAACACTCCCTGGCCTTCTGTTTCTTGATTCCTTAATTTTGAG
ATAAGACCGTCCCTAGCAGTGAGGCCTCGGCCTCTGTTCATTTAACTTCTCAAACCAAAC
TAGCCCTAATTCAGTTCACCCCAGAGCATCACCTGGTTTTATTTTTATTTTTTTATTTTT
TTATTTATTTTTTTTTTTTTTGCAGCCTGAAATTTTAAGTCACCGTTTGTCTCCCTCACC
AGGGTGTGAACTGCCCCGAGGGCAGAGACCTCCCGTTTTGTTTTCCAGCGCCTTGAGCCA
GCTTGACTTTTTACAAATGCTGAGTGAGACGTGTCGGTGGCTCCCAGTGCACTTGGCAGA
GTGAGCCGCAGCCAGCTGGGCGCTCCAGGCAGGACACAGTGGCCTCCACGAGGATCCCTT
ACCATTACTGTGCGGCCGCGCTCCGTAGGTCAAGCCGCTCTTACCAAGCGTCTTTCTGCC
TTTCTGTTCCCCCTCAGAGCTGTGCGCGCTGCAGAAGGCGGTGGAGCTGGAGAAGACAGA
GGCGGACAACGCGGAGCGGCCCCGGGCGCGACGGCGGAGGAAGCCGCGCGTGCTCTTCTC
GCAGGCGCAGGTCTATGAGCTGGAGCGGCGCTTCAAGCAGCAGCGGTACCTGTCGGCCCC
CGAACGCGACCAGCTGGCCAGCGTGCTGAAACTCACGTCCACGCAGGTCAAGATCTGGTT
CCAGAACCGGCGCTACAAGTGCAAGCGGCAGCGGCAGGACCAGACTCTGGAGCTGGTGGG
GCTGCCCCCGCCGCCGCCGCCGCCTGCCCGCAGGATCGCGGTGCCAGTGCTGGTGCGCGA
TGGCAAGCCATGCCTAGGGGACTCGGCGCCCTACGCGCCTGCCTACGGCGTGGGCCTCAA
TCCCTACGGTTATAACGCCTACCCCGCCTATCCGGGTTACGGCGGCGCGGCCTGCAGCCC
TGGCTACAGCTGCACTGCCGCTTACCCCGCCGGGCCTTCCCCAGCGCAGCCGGCCACTGC
CGCCGCCAACAACAACTTCGTGAACTTCGGCGTCGGGGACTTGAATGCGGTTCAGAGCCC

FIG. 4B (3)

CGGGATTCCGCAGAGCAACTCGGGAGTGTCCACGCTGCATGGTATCCGAGCCTGGTAGGG
AAGGGACCCGCGTGGCGCGACCCTGACCGATCCCACCTCAACAGCTCCCTGACTCTCGTG
GGGAGAAGGGGCTCCCAACATGACCCTGAGTCCCCTGGATTTTGCATTCACTCCTGCGGA
GACCTAGGAACTTTTTCTGTCCCACGCGCGTTTGTTCTTGCGCACGGGAGAGTTTGTGGC
GGCGATTATGCAGCGTGCAATGAGTGATCCTGCAGCCTGGTGTCTTAGCTGTCCCCCCAG
GAGTGCCCTCCGAGAGTCCATGGGCACCCCCGGTTGGAACTGGGACTGAGCTCGGGCACG
CAGGGCCTGAGATCTGGCCGCCCATTCCGCGAGCCAGGGCCGGGCGCCCGGGCCTTTGCT
ATCTCGCCGTCGCCCGCCCACGCACCCACCCGTATTTATGTTTTTACCTATTGCTGTAAG
AAATGACGATCCCCTTCCCATTAAAGAGAGTGCGTTGACCCCGCACGTGTGCTTCTTTCA
GCTTGCGGCGCTTCAGAAGCAGGAGAGAGGTGGCCGCCCGGGACTGGTCTCAGATCTCAG
GCACAGGCATTCCCTGAGCAAATTGATAACATTGATACTAATAAAACCTAACCCTTGCTG
GAACCATACTGGTTCCGTGTCGGGCACTTTCTGAGATTGTCTCATATAATCCTCAATAAT
CCAAAAAAAAAAAAAATCCTAAAGTTTAGAAGCTGAGGCCCGGAGAGGTTTAATGACTTAC
CTGCGAGCAAATAGCCAGTACTAGTCGAACTCTGGTTAAATTCAGGATGCCTCACTTCAG
AGACCGCCTTCCCTGTGCTCCCAAGCTCCCCTCCTTGAATCCTAATGTGTGCCAGGCACG
GTTCCAGGCACTGGGCATTAAATGGACAAGCAAAAGAACCTGGGCCCTCTGTAGCTGGAG
AGCACCGTGATCATCCCACTTAAAAGAACTCCTTAACCTGTTTCCAAGATGGNAAAAGCC
AAGAANCCAAAGCCCTTGGGNAAGCGTTCTCAAGGGTCCTCANATGCCCCAAATGCCACG
TCGGGGGCTCAACANCTNGCCCGTTGGAACTGAATGCCNANGGTGGGCCCCAAANAAGGN
TCCTGCGGGATGGNGCTCAACTCCAAGCTGTGGTGAAGGCCCATAAAATTCAAATGGGCC
AAGGGGAGCCCCCTAAAGCCCTAAACCTTCNGGGGGTCCNTTCCCTAAGGGCATTTAANT
TTACCAAAAGTTTGGNCAAANAATGTTTCCAATGGNCCNGATTTTATNGANGGGNAAAAC
TGGNGGGCAACCGAAATCCAGTTTAAACCCGGGTTGTTT (SEQ ID NO.: 5)

FIG. 5A

AGGCCCCCCG CACCCTCATC CTGGCTCCCG CCCCTTCTCT CCACCCTCCC
GGACCCCTAA AGGGGCGGCG GGGCCCAAGC CGAGGGCGCT GCGCCTGACC
CCGAGCGGAA GGGCCCCAGT CTAGGTCCTA ATGCGGGTGG CGTCTCCTTT
GACAGGCGGC GTTTGGGGAC AACAGCGGGG ACGAGAGATA AGGTGACATA
CCAGAGCAGA TTTGGTGCGC GCGCTGATAC TCCTCTCCCG ACAGGAAACG
CGGAGCTATT TAAAAGACCC TATCGATTAC TTTATCTTTC CTGGAAAGCT
TCTTGCGGAG AGACAAAAGA TGTTCCCTGC CTAAAGACAC AAGGCCACAC
AACGGAGGGT CTGCACAGGC GACGC (SEQ ID NO.: 1)

TGCTCCTTT TAAGGGCTTG AATGTCTGCA ACTGTCATGT GTACACTTAA
AG (SEQ ID NO.: 2)

FIG. 5B

AGGCCCCCCG CACCCTCATC CTGGCTCCCG CCCCTTCTCT CCACCCTCCC
GGACCCCTAA AGGGGCGGCG GGGCCCAAGC CGAGGGCGCT GCGCCTGACC
CCGAGCGGAA GGGCCCCAGT CTAGGTCCTA ATGCGGGTGG CGTCTCCTTT
GACAGGCGGC GTTTGGGGAC AACAGCGGGG ACGAGAGATA AGGTGACATA
CCAGAGCAGA TTTGGTGCGC GCGCTGATAC TCCTCTCCCG ACAGGAAACG
CGGAGCTATT TAAAAGACCC TATCGATTAC TTTATCTTTC CTGGAAAGCT
TCTTGCGGAG AGACAAAAGA TGTTCCCTGC CTAAAGACAC AAGGCCACAC
AACGGAGGGT CTGCACAGGC GACGCACAAT TCGGCGCGGG GAAAGCAAAA
ACACACTGAC GCTTAGAGTG CACAAACGTG TGTGTTCCCA GAGCAGCTCC
AGAGTGCGGC AGGGACGCTG GGGGCGGCGA GGGGCACCCA CAGTATGGTC
TTCTGTGCCC TTGGAAAGTT TTTTTTCACC GTATGCGCGT AAAACACGCA
CACACAGAGA AAGTGACTGT GCACTTAGGG CGCCTGTGTG TACCCGTGTC
GTTTTAGCGA ATTTAAAGCA CATCAGGCCG GGCGCCATGG CTCACGCCTG
TAATCCCAGC ACTTTAGGAG GCCGAGGCGG GCCGATCACC TGAGGTCGGG
AGTTCGACAC CAGCCTGGCC AACATGGTGA AACCCTGTCT CTACAAAAAA
TACAAAAATT AGCCGGGCAT GGTGATGCGT GCCTGTGATC CCAGCTACTC
GGGAGGCTGA GGCAGGAGAA TCGCTTGAAC CCGGGAGGCG GAGGTTGCAG
TGAGCCGAGA TCACACCACT GCACTCCAGC CTGGGCGACA AGAGCGAAAT
TCCGTCTAAA AAAATAAAAT AAAATAAAAT GATAATTAAG CCCATCAACT
CACATTCAAA GCGGTTACTG GTGGTTGTAA TGTATCCATA GACACAGGTC
TAAAATGTAA ACGCTCCATT GTGCTCCTTT TAAGGGCTTG AATGTCTGCA
ACTGTCATGT GTACACTTAA AG (SEQ ID NO.: 3)

FIG. 5C

AGAGAAATCA TTACCCGATT CACAAAGAGC ATAGAGAGTG TAACAGTCAC
TGATCTTGTT CAAATAGGGA GAGTTTTTTT TCCTTCCCTT TTTGTAACAC
CTGACCCACA GGACTGACAG TTCTAGGAAG CCCCCTTACC CGAAAATAGG
AAATAAATCC TTGCCACCTT GATTTGCAAG GGCAATGCTA ATTTTTTTCT
TTCTCCAGAG CTCTCAAAAA AAAAAAAAAA AAAACCTTAC TAAAAACAGG
GATCCCGGAT GTAGCCTCGA TGTCCCCCAT TAAACGGTAA TATTTCAGGC
GTCCGCTCAC ACTAATCTTT CAAACTGTCA TCGCGAGCCG CCTGGCCAGC
AGATTCACTT AACAGCGCTC CCAGGACCCT CGTTCCGAGC TCTTTTCAGC
GAGACATTTA ATTGAATCGG ATGTGGCTCG TTTGCCAGAC GTCACCGCCT
CGGCGATAGG CATCCTCTCC AACGACAC (SEQ ID NO.: 6)

FIG. 6

Transgenic Constructs of the Human Csx/Nkx2-5 Enhancer

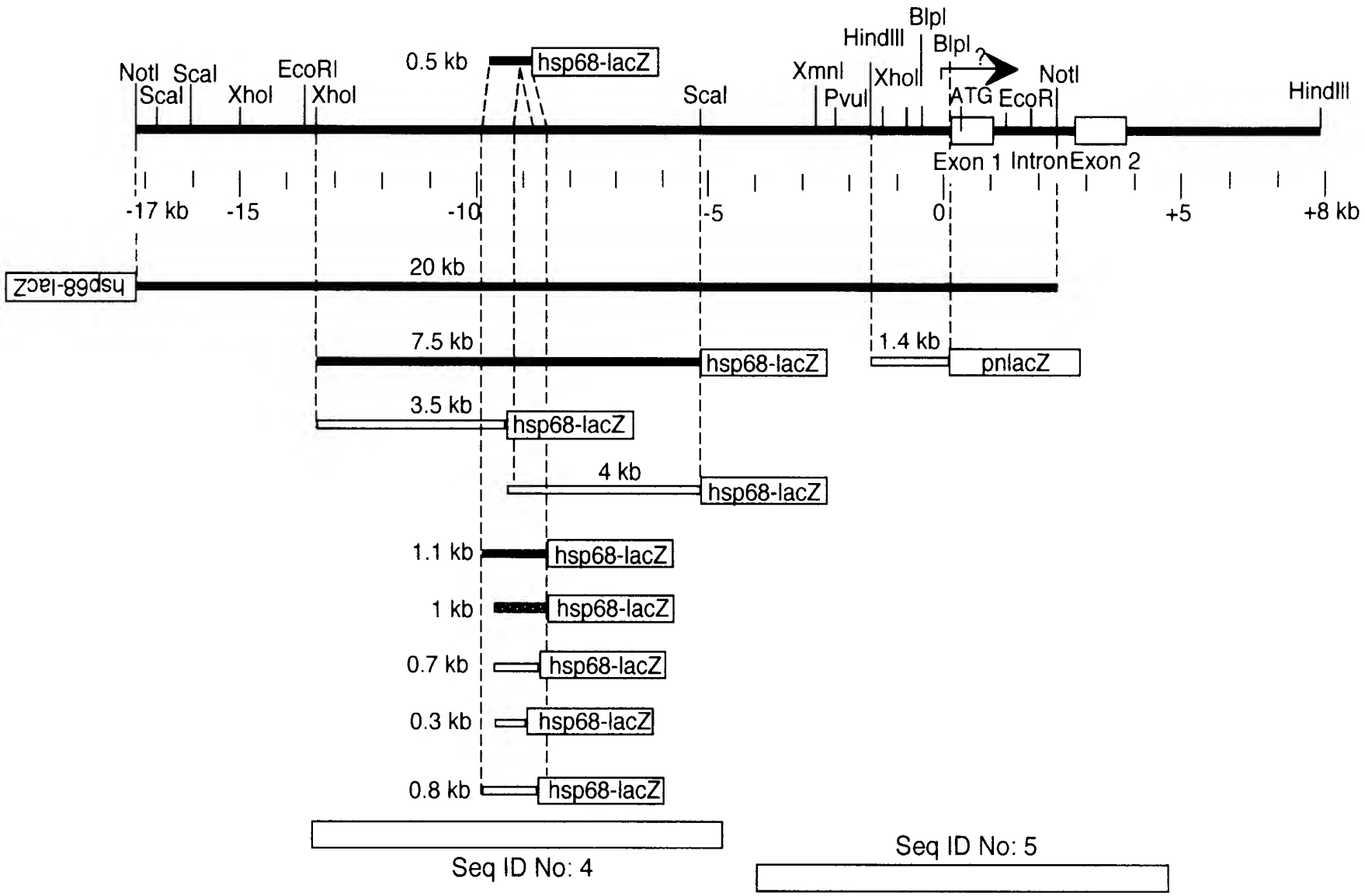
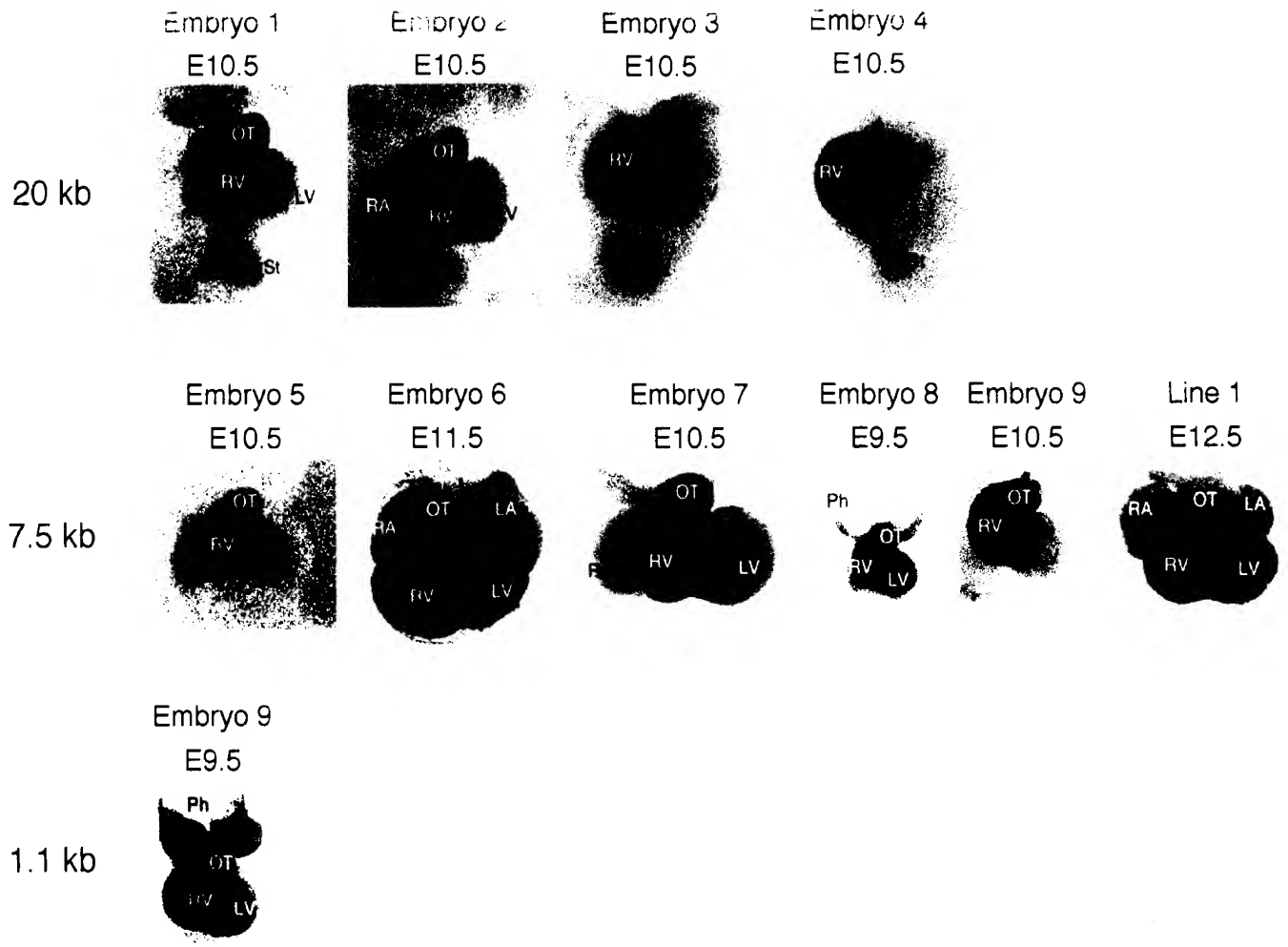


FIG. 7

Transgenic Analysis of the Human Csx Enhancer Sequence

Constructs	# of Transgenes	Enhancer positives (Cardiac : Ectopic)[1]
20 kb	8	4 : 0
7.5 kb	8	6 : 1
promoter-proximal 4 kb	7	0 : 1
promoter-distal 3.5 kb	6	0 : 0
1.1 kb	8	3 : 1
1.0 kb	10	1 : 2
0.7 kb	8	0 : 3
0.3 kb	11	0 : 6
0.8 kb	6	0 : 1
0.5 kb	2	2 : 0

1. Each embryo was classified into either 'cardiac' or 'ectopic' judged upon the extent of similar to the endogenous Csx expression pattern.

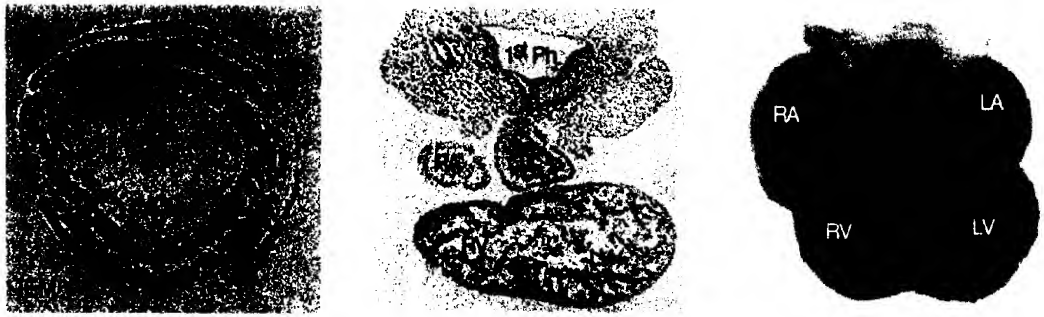


RA; Right Atrium LA; Left Atrium RV; Right Ventricle LV; Left Ventricle

Ph; Pharyngeal Arch St; Stomach OT; Outflow Tract

Cardiac Expression of the 7.5 kb hCsx Enhancer-hsp68-lacZ Construct

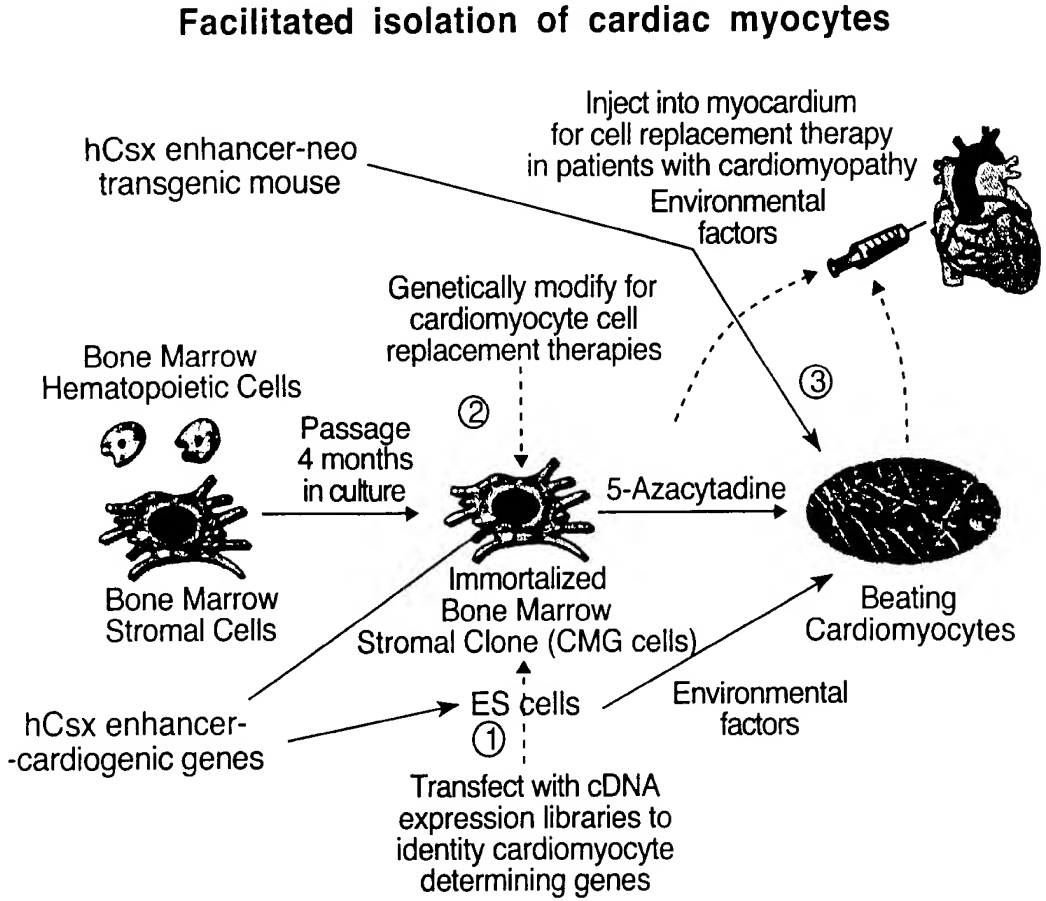
E7.5 E9.5 E10.5 E12.5 3 Days 4 Weeks



E7.5 E10.5 E12.5

RA; Right Atrium LA; Left Atrium
RV; Right Ventricle LV; Left Ventricle
OT; Outflow Tract Ph; Pharyngeal Arch
IEM; Intra Embryonic Mesoderm
NG; Neural Groove

FIG. 10


Facilitated isolation of cardiac myocytes
hCsx enhancer-neo transgenic mouse
Inject into myocardium for cell replacement therapy in patients with cardiomyopathy
Environmental factors
Genetically modify for cardiomyocyte cell replacement therapies
Bone Marrow Hematopoietic Cells
Passage 4 months in culture
②
③
5-Azacytadine
Bone Marrow Stromal Cells
Immortalized Bone Marrow Stromal Clone (CMG cells)
Beating Cardiomyocytes
hCsx enhancer--cardiogenic genes
ES cells
①
Environmental factors
Transfect with cDNA expression libraries to identity cardiomyocyte determining genes